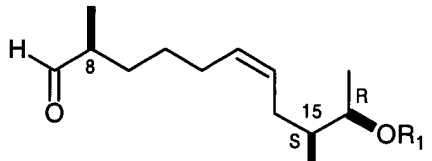
Detailed Description of the Invention

Total Synthesis of Epothilone A

Epothilones B, **1** and A, **2** (shown above) contain a 16 membered lactone ring with hydroxyl groups at C-3 and C-7, ketone at C-5, epoxide at C-12,13 and an aryl containing side chain at C-16. Both lactone and ketone groups contain β-hydroxy functionality which can presumably be installed via asymmetric aldol condensation. Overall, Epothilone is a typical macrolide possessing an array of alternating methyl and hydroxyl groups of varying stereochemistries.

We have envisioned the deconstruction of **1** and **2** retrosynthetically as shown in Figure 1 (Scheme I). The underlying key contruction step in our approach employs a copper (I) promoted Normant coupling of the monoterpene-derived Grignard of **6**, with propyne followed by trapping of the resulting organocopper intermediate with Sharpless epoxide **5**. This procedure allows for a rapid preparation of the aldehyde **7** required for Aldol condensation with the known keto-acid **10**, furnishing the acyclic acid **11**. Macrolactonization to **12** followed by simple functional group manipulations is expected to provide Epothilone B.

A second retrosynthetic scheme we developed was based on the production of Epothilone A **2** by alkyne opening of an epoxide, which later lead stereoselectively to a cis-olefin and thereby the 12,13-cis epoxide moiety as shown in Figure 2 (Scheme II). A few aspects of this work have been published (Bijoy, P. and M.A. Avery, *Synthetic studies directed towards epothilone A: enantioselective synthesis of a C7-C15 carboxaldehyde segment.* Tetrahedron Lett., 1998. **39**(3/4): p. 209-212), and application to the total synthesis of Epothilone A, **2**, has been pursued in parallel to the alternate route outlined in Figure 1 (Scheme I). Apart from the aldehyde **21**:



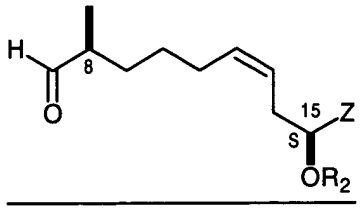
21, R_1 = DPS, R_2 = TBS

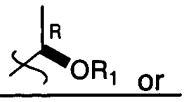
reported in our earlier work we also prepared the aldehydes **20a** and **20b** essentially having different protecting groups at the secondary hydroxyl groups, as shown in Figure 3 (Scheme III).

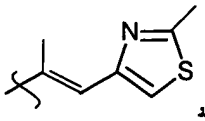
The synthesis of **20a** and **20b** shown in Figure 3 (Scheme III) involves preparation of the alkynylalane **14** from the alkyne **13**, that upon opening of **5** and dil.HCl quench gave the diol **15.** Selective reduction of the alkyne **15** (Lindelar reduction) provided the required *Z*-olefin **16**. A sequence of events transforms **16** into iodide **17**: selective tosylation at the primary alcohol; protection of the secondary alcohol as the TBS (*tert*-butyldimethylsilyl) occurs without disturbing the primary tosylate, and finally, NaI displaces the tosylate to give the iodide **17**. Alkylation of this iodide with the enolate of propionyl amide **18** prepared from the (-)-camphorsultam afforded the homologated material, auxillary intact, **19**. DIBAH reduction of the adduct **19** resulted in the aldehydes **20a** and **20b**. The aldehydes **20a** and **20b** are the desmethyl counterparts to aldehyde **7** in Figure 1 (Scheme I). The overall process is 7 steps from pentynyl derivative **13**.

Alternatively, the side-chain thiazole ring could be installed to provide the aldehyde **29** as outlined in Figure 4 (Scheme IV). In this approach treatment of **16a** with MEM-Cl yielded the bis-MEM ether. Desilylation of the bis-MEM ether with fluoride ion gave **22**, oxidation of which then provided the ketone **23**. Horner Emmons Reaction of **23** with the phosphonate anion of **24** then afforded the diene **25**. Remarkably, **25** could not be deprotected readily under expected conditions, but required concentrated HCl solution to effect transformation into the diol **26**. The primary alcohol of diol **26** was smoothly tosylated, and the secondary alcohol silylated with TBSOTf. Upon Sn2 displacement of the primary toxylate, the iodide **27** was isolated as a light yellow, reasonably stable oil. Alkylation of the iodide with the anion of sultam **18** gave adduct **28**. Reduction to the adduct **28** with DIBAH provided the requisite aldehyde **29** which was identical in all respects compared to the one reported by Nicolaou (Nicolaou, K.C., *et al.*, *Total Syntheses of Epothilones A and B via a Macrolactonization-Based Strategy.* J. Am. Chem. Soc., 1997. **119**(34): p. 7974-7991).

The aforementioned aldehydes **7**, **20a**, **20b**, **21**, and **29**, and stereoisomers thereof, can be represented by the following general formula:



where Z is 

or 

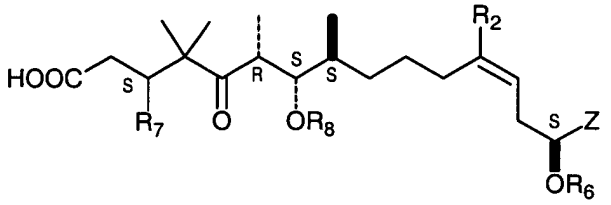
, R_1 is TBS or DPS and R_2 is TMS, TBS. Stereoisomers of these aldehydes can be similarly represented.

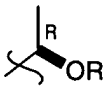
For aldol condensation required by Scheme I, the silyl-protected keto-acid **10** was required. As reported by a unique route, Nicolaou (Nicolaou, K.C., *et al.*, *Total Syntheses of Epothilones A and B via a Macrolactonization-Based Strategy.* J. Am. Chem. Soc., 1997. **119**(34): p. 7974-7991) reported that the silyl-protected keto-acid **10** had a rotation ($[a]^D$) of +16.1°. According to De Brabander (De Brabander, J., S. Rosset, and G. Bernardinelli, *Towards a synthesis of epothilone A. Rapid assembly of the C(1)-C(6) and C(7)-C(12) fragments.* Synlett, 1997(7): p. 824-826), this acid could be prepared from the N-propionate of the (+)-Sultam **30** as outlined in Figure 5 (Scheme V). De Brabander reported a rotation value for sultam **33** of +119°, depicted the alcohol stereocenter as *S*, and deposited the crystal structure in the Cambridge Crystallographic Database (CCD). However, perusal of structure **33** in the CCD shows clearly that the alcohol stereocenter is *R*, opposite of that drawn in the paper.

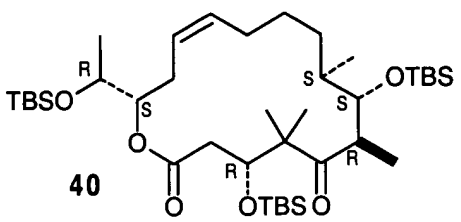
Furthermore, no rotation value was given for the acid **34** except stating that this acid was previously reported by Nicolaou. Without confirming the X-ray results reported by De Brabander by logging into the CCD, one would assume the correct acid to be derived from Scheme V. In fact, when we prepared the TBS-acid **34** as outlined, the rotation value we obtained was in good agreement with Nicolaou at +17.4°. DeBrabander later corrected his first publication. De Brabander, J., S. Rosset, and G. Bernardinelli, *Towards a synthesis of epothilone A. Rapid assembly of the C(1)-C(6) and C(7)-C(12) fragments. [Erratum to document cited in CA127:234203].* Synlett,

1998(6): p. 692; De Brabander, J., S. Rosset, and G. Bernardinelli, *Towards a synthesis of epothilone A. Rapid assembly of the C1-C6 and C7-C12 fragments. [Erratum to document cited in CA127:234203].* Synlett, 1998(3): p. 328.

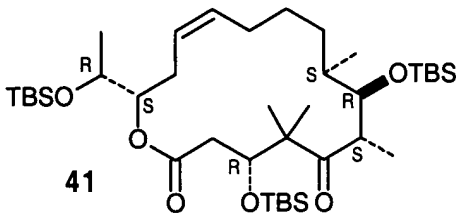
When the TBS acid we assumed was **10** (shown in Figure 5 (Scheme V)) was condensed with aldehyde **21**, reduced product **35** was obtained as shown in Figure 5a (Scheme Va). In the course of investigations, it was determined that the bulky diphenyltertbutylsilyl (DPS) & tertbutyldimethylsilyl (TBS) groups were responsible for this unexpected result. When the aldehyde **20b** (TMS replaces TBS) was used, the aldol reaction did take place but the yields were only moderate. On the other hand the aldol reaction with **20a** went much more smoothly to give a mixture of 4 diastereomeric aldol adducts in good yields. In order to convert these linear products to materials we could match to literature, we trapped the intermediate aldolates with TBSOTf, and the labile TMS group was then lost during chromatography to give **36-39** as shown in Figure 6 (Scheme VI). These acids, **36-39**, as well as stereoisomers thereof, may be represented by the following general formula



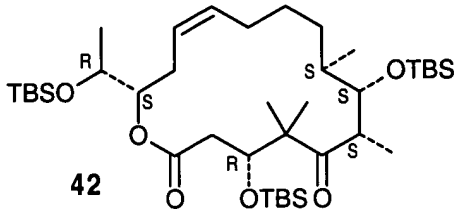
where Z is  and where R_1, R_7, and R_8 are each TBS. The isomers as a mixture were cyclized with $Cl_3C_6H_2COCl$, pyridine, DMAP to afford lactones **40-43**:



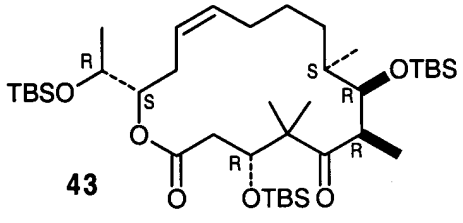
40



41

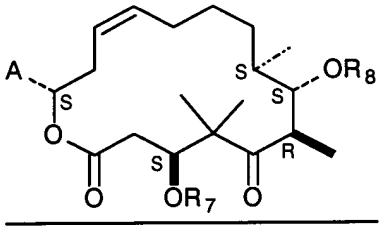


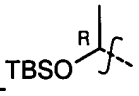
42

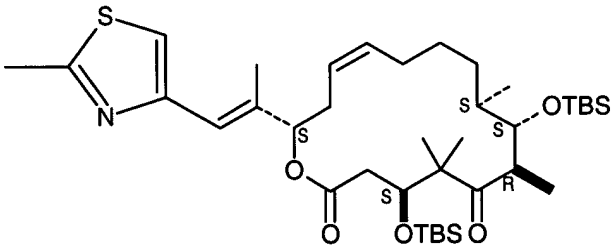


43

The lactones 43 and stereoisomers thereof, may be represented by the general formula

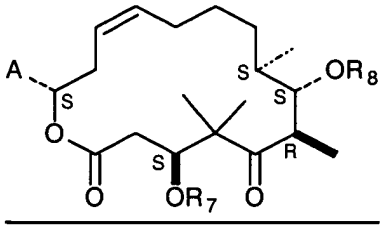


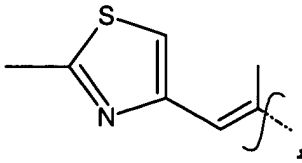
where A is  , and R_7 and R_8 are each TBS. As indicated in Figure 7 (Scheme VII) and Figure 8 (Scheme VIII), each diastereomer was then selectively deprotected, oxidized to methyl ketone (evident by NMR), and finally, reacted with Horner-Emmons reagent **24** to furnish penultimate intermediates on the way to a route to Epothilone A reported by Nicolaou. In this report, spectral data for **46:**



46, Nicolaou

was slightly different from each isomer brought forward, intermediates **45,47-49** shown in Figure 7 (Scheme VII) and Figure 8 (Scheme VIII). Intermediate **46** may also be represented by the following general formula



where A is 

, and R_7 and R_8 are each TBS. As should be understood, intermediates 45 and 47-49, and their stereoisomers, may be similarly represented. None of these products matched known material. Each stereocenter was individually checked, including the synthesis of the α-methyl diastereomer of the aldehyde **29** to make sure we have the correct stereochemistry. Finally, we checked the lactones from Daneshevsky's synthesis of epi-epothilones, and matched lactone **45** with known material. This clearly indicated that the keto-acid reported to be **10** was incorrectly assigned by De Brabander and was in fact keto-acid **34**. This also confirms the error in reporting the sign of the optical rotation of **10** by Nicolaou.

With this revelation at hand, we prepared **10** with the opposite sign of rotation as reported by Nicolaou, as shown in Figure 9 (Scheme IX), by condensation with the N-acetyl derivative **51**, prepared from (-)-sultam (**50**) and acetyl chloride, with aldehyde **9**. After silylation and removal of auxillary, we obtained **10** with sign of rotation opposite that reported by Nicolaou (Scheme IX).

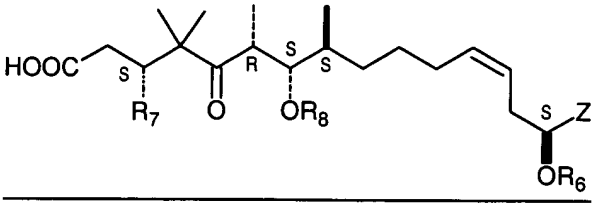
As final proof of this reassignment to the sultam route to **10**, we condensed bonafide **10** with aldehyde **29** as shown in Figure 10 (Scheme X). The resulting acids **53** and **54** were identical to reported materials by proton and carbon NMR, and the

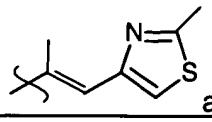
signs of rotation were as reported. Finally, selective deprotection of **54** to give the alcohol **55** was followed by cyclization to afford the reported precursor to Epothilone A, **46**. This formally completes the synthesis of Epothilone A.

In order to reduce the total number of steps en route to the epothilones, the trianion of acid **56** has been examined in a model system such as benzaldehyde and gave outstanding chemical yields, but in a 1:1 ratio of syn,syn to syn,anti. With **21** however, **56** led to sole production of the reduced aldehyde, alcohol **35**, as shown in Figure 11 (Scheme XI). On the other hand reaction with **29** resulted in the aldol products **57** and **58**. Removal of the TBS group of **58** using TBAF afforded the triol acid **59**, which on macrocyclization gave **60**, the precursor to Epothilone A (Scheme XI).

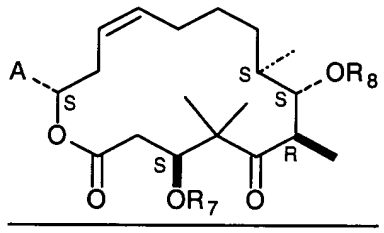
Presumably, macrolactonization of the triol-acid **59** gave the desired product based on the relative rates of 4- vs 8- vs 16-membered ring closures, as indicated in Figure 12 (Scheme XII). The relative rates are 0.58, 1.5 X 10^{-4}, and 3 X 10^{-3}, respectively, clearly indicating an initial preference for β-lactone formation. Casadei, M.A., C. Galli, and L. Mandolini, *Ring-Closure Reactions. 22. Kinetics of Cyclization of Diethyl(w-Bromoalkyl)malonates in the Range of 4- to 21- Membered Rings. Role of Ring Strain.* J. Amer. Chem. Soc., 1984. **106**: p. 1051-1056. However, it is also known that β-lactones are excellent active esters and react with alcohols to give ring-opened esters. Lactonization conditions applied to **59** probably formed the β-lactone **61**, but subsequent *in situ* trans-lactonization resulted in formation of the desired 16-membered lactone **60**.

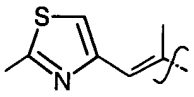
Acids **53** and **54**, alcohol **55**, aldol products **57** and **58**, triol acid **59**, discussed above, and their stereoisomers, may be represented by the common following formula

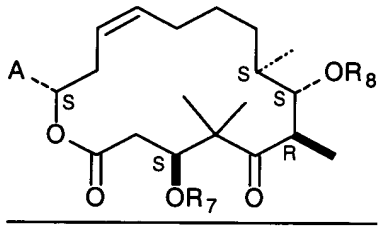


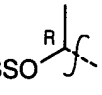
where Z is  and R_6 is TBS, H, TMS, or PMBM, and where R_7 and R_8 are either H or TBS.

Similarly, reaction of **10** with the aldehyde **20a** resulted in the aldol adducts **62-65** which on further transformations as outlined previously afforded the corresponding cyclic lactones **46**, **70-72**, as shown in Figure 13 (Scheme XIII). These lactones, 70-72, as well as their stereoisomers, may be represented by the following general formula



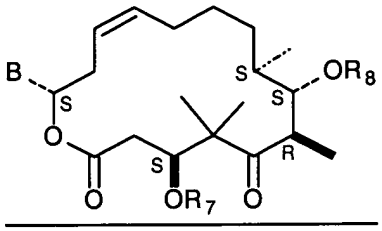
where A is  , and R_7 and R_8 are each TBS. Similarly, interemediates 66-69 and their stereisomers may be represented by the following general formula

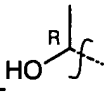


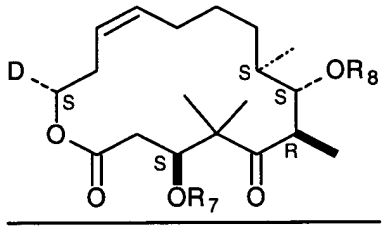
A is  , and R_7 and R_8 are each TBS.

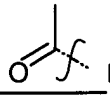
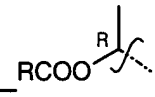
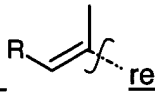
With reference to Figure 14 (Scheme XIV), in all of the above cases (e.g. Schemes VII, VIII, XII, etc.), the corresponding 3S alcohols **73** and ketones **44** provide starting materials which can be derivatized and the resulting products **75** and **78** used as bioactive substances (R = alkyl, aryl, heterocyclic). Obviously, related 3R intermediates **74** and **77** can be processed similarly to furnish the 3R products **76** and

79. Diastereomeric materials can be carried forward in the same fashion. The alcohols 73, and their stereoisomers, may be represented by the general formula

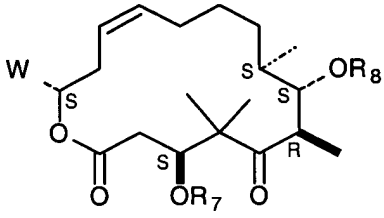


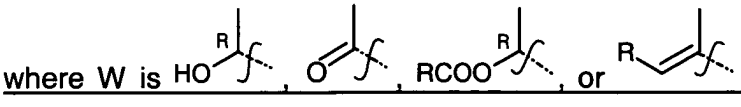
where B is  and R_7 and R_8 are each TBS. As should be understood, R_7 and R_8 could also be H. The ketones 44 and resulting products 75 and 78, and stereoisomers thereof, may be represented by the general formula



where D is   and  respectively, R is alkyl, aryl, or heterocyclic, and R_7 and R_8 are each TBS.

Collectively, these alcohols, ketones, and aldol products, as well as their respective stereoisomers, may be represented as follows:



where W is  , R is alkyl, aryl, or heterocyclic, and R_7 and R_8 are each TBS.

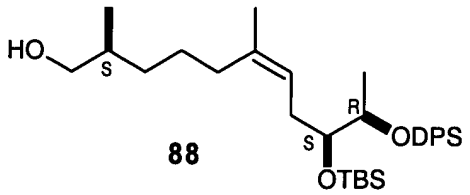
Total Synthesis of Epothilone B

Total synthesis of **1** via Scheme I is based upon a Normant reaction in which an acetylene derivative such as propyne or TMS-acetylene was coupled to a Grignard reagent in the presence of Cu(I), and the intermediate cuprate was then used as a nucleophile to open a Sharpless epoxide such as **5**. Numerous cases were examined to find the best conditions and protecting groups to facilitate the overall synthesis, and started with the addition of the TIPS protected Grignard **80** to propyne as outlined in Figure 15 (Scheme XV). Addition of Cu(I) to the Grignard derived from **80**, followed by propyne resulted in an intermediate vinyl cuprate **80a** that could not effect opening of epoxide **5b**, but could be quenched with iodine to furnish the *Z*-vinyl iodide **81** in excellent yield. Metallation of the vinyl iodide with alkyl lithium and metal exchange with an aluminum chloride provided a sufficiently reactive vinylalane which effected opening of the DPS protected epoxide **5b** to give the differentially protected triol **82**. Desilylation of **82** with dilute acid and selective tosylation gave the tosylate **84**, that upon silylation with TBSOTf gave disilylated tosylate **85**. Upon Sn2 displacement with iodide, the stable iodide **86** was formed and alkylated with the propionosultam **18** to give **87**, by analogy to formation of **20**. Overreduction with lithium aluminum hydride gave alcohol **88**, and finally, reoxidation with pyridine-SO_3 complex furnished the target aldehyde **21a**.

An alternative approach to the preparation of the aldehyde **21** which bypassed the iodoalkene intermediate **81** was examined involving addition of an olefinic Grignard derived from **89** at the outset instead of the TIPS ether **80**, as shown in Figure 16 (Scheme XVI). Apparently, the presence of a g-TIPSO moiety had a detrimental effect on the ensuing epoxide opening via cuprate intermediate **80a**. On the other hand, the cuprate intermediate **89a** suffered no such limitation after ligand exchange with pentynyl lithium, and smoothly effected opening of **5b** to furnish the alcohol-diene **90** in excellent

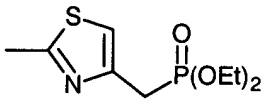
yields. Conversion to the known tosylate **85** was then accomplished as follows: Silylation gave the TBS ether **91**; oxidation of the less hindered terminal olefin was achieved with AD-mix α, and the resulting diol cleaved to aldehyde **92** with periodate. Finally, reduction to alcohol and tosylation gave **85**.

Unfortuantely however, aldehyde **21a** behaved identically to **21** in attempted aldol condensation, giving reduction product **88:**



88

Therefore, as before, some adjustment had to be made to the protection scheme in order to achieve the aldol condensation. As shown in Figure 16 (Scheme XVI), use of **5a** instead of **5b** gave the expected opening product **91** that could be protected with a smaller silyl group, TMSOTf to furnish the bisprotected diene **93**. AD mix as before, and glycol cleavage gave aldehyde **95**, that could be reduced and tosylated to provide **96**. Following the reaction of Figure 17 (Scheme XVII) as before with DPS/TBS protection, now substituting TBS/TMS **96** allowed for the production of aldehyde **100**. With less hydrophobic steric bulk at the terminus of the side chain (e.g. DPS vs. TBS), the aldol condensation occurred more readily than was the case in the Epothilone A series, Figure 13 (Scheme XIII). Thus, upon treatment of **100** with **10**, aldol adducts could be obtained and silylated *in situ* as before, becoming immediately ready for cyclization after silica gel chromatography. As shown in Figure 18 (Scheme XVIII), from this mixture, **104** (or **11** from Scheme I) cyclized in the usual manner to furnish the precursor to Epothilone B, **105**. Selective desilylation as before, giving a free alcohol **106**, and oxidation gave the ketone **12**, and Horner-Emmons Reaction with **24:**

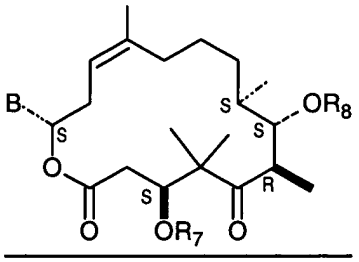


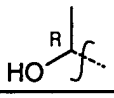
gave the bis-TBS ether of deoxyepothilone B, **107**. This is a known compound that has been converted to Epothilone B previously. Nicolaou, K.C., *et al.*, *Total Syntheses of*

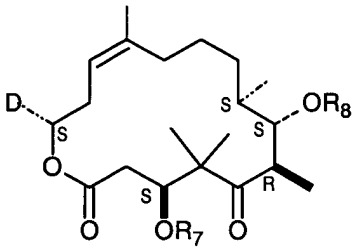
Epothilones A and B via a Macrolactonization-Based Strategy. J. Am. Chem. Soc., 1997. **119**(34): p. 7974-7991.

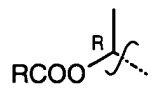
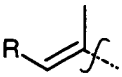
Clearly, as before in the Epothilone A series, Figure 14 (Scheme XIV), both alcohol **106** and ketone **12** serve as excellent precursors for the production of analogs as outlined in Figure 19 (Scheme XIX).

Alcohol **108**, as shown in Figure 19 (Scheme XIX), and stereoisomers thereof, may be represented by the general formula



where B is  and R_7 and R_8 are each TBS. In addition, chemical compound **109** and resulting products **110** and **112** and stereoisomers thereof may be represented by the general formula



where D is   and  respectively, R is alkyl, aryl, or heterocyclic, and R_7 and R_8 are each TBS. Again, not only can the 3*S* series be represented in this chemistry, but so can the 3*R* diastereomers. A variety of analogs of Epothilone B can be prepared in the side-chain such as esters **112/113** or styrenes or alkenes **110/111**.

Another alternative to the production of such differentially protected side-chain diols is shown in Figure 20 (Scheme XX). In this instance, the monoterpene *S*-dihydromyrcene **114** was employed for its chirality at the methyl position by ozonolytic treatment and reductive workup to furnish degraded alcohol **115**. Conversion to the bromide **116** was straightforward, and ensuing Normant reaction as before provided the extensively homologated diol-diene **117** or **118**, depending on whether epoxide **5a** or **5b** was used.

Protection in this case was with a TMS group when DPS was present from **5b**, alternatively, when the TBS epoxide was used resulting in **118**, then a para-methoxybenzyl (PMB) group was installed to provide **120**. Oxidation as before of either terminal alkene with ADmix followed by glycol cleavage with periodate gave the aldehydes **121** or **122**. Either of these aldehydes could be used in aldol condensation with acids such as **10** or **56** to provide cyclization precursors to either analogs or Epothilone B.

An additional and intriquing approach to the Epothilones involved the use of 4-methylpentyl bromide in the Normant reaction, shown in Figure 21 (Scheme XXI). In this case, the usual procedure gave **124** after water workup. However, the intermediate alkoxide could be capped with TMSOTf to furnish the bisprotected compound **125** directly. Alternatively, **124** could be blocked in a separate step with TMSOTf to arrive at the same compound **125**. Furthermore, as shown in Figure 22 (Scheme XXII), a PMB group could be placed on this position in a one pot procedure by adding PMB-Br to the cuprate intermediate, to access the PMB ether **129** directly. Diene **125** (Figure 21, Scheme XXI) was then hydroborated with bis(isopinocampheyl)borane to give, after oxidative workup with hydrogen peroxide, the *S*-methyl alcohol **126**. Cr(VI) workup (e.g. with PCC) gave the desired aldehyde **100** directly, or separate oxidation of the alcohol **126** afforded **100**. Conversions of **100** including its processing to natural product have been discussed (*vide supra*).

An alternative that incorporates the thiazole ring earlier in the synthesis is shown in Figure 22 (Scheme XXII). As discussed above, the PMB ether **129** can be formed in a one pot procedure. It can be converted directly into the ketone **131**, a direct precursor

for chiral hydroboration, or can be removed separately to give alcohol **130** which can be oxidized to the ketone **131**. In either event, the ketone **131** undergoes Horner-Emmons reaction to give the triene **132**. Now, in similar fashion to before, hydroboration with $(Ipc)_2BH$ can be followed up with either H_2O_2/NaOH to give alcohol **133**, or with Cr(VI) to give aldehyde **134** directly. The alcohol **133** can be oxidized separately to furnish aldehyde as a second route to **134**, a known compound whose spectral data was identical to ours. Nicolaou, K.C., *et al.*, *Total Syntheses of Epothilones A and B via a Macrolactonization-Based Strategy.* J. Am. Chem. Soc., 1997. **119**(34): p. 7974-7991.

The ensuing aldol condensation of **134** gave products identical to those reported, and subsquent conversions were uneventful. For the precedented reactions, dianion from **10** reacted with known **134** to give either the alcohol **135** (water workup) or the tri-TBS ether **137** (TBSOTf quench, or separate reaction). Either fully silylated acid **138** (literature) or fully desilylated acid **137** (novel) could be cyclized to furnish lactones **107** (literature) or **139** (literature). Their conversion to natural product is known, (Nicolaou, K.C., *et al.*, *Total Syntheses of Epothilones A and B via a Macrolactonization-Based Strategy.* J. Am. Chem. Soc., 1997. **119**(34): p. 7974-7991) formally completing the total synthesis of Epothilone B.

A straightforward approach to Epothilone B involves the preparation of ketone **140** (e.g. from alcohol **128**), and effecting Horner-Emmons condensation with anion from **24** to furnish elaborated epoxide **141**, as shown in Figure 23 (Scheme XXIII). Normant reaction as before with bromide **123** and propyne, quenching the vinyl cuprate intermediate with **141**, and finally, trapping of the alkoxide final intermediate with TMSOTf, gave the triene **143**. Aldol condensation with the trianion **56a**, and simultaneous chromatography-deprotection provided the triol-acid **59**. Cyclization as before gives Deoxyepothilone B **60**, which could be epoxidized to afford the natural product **1**. Several points worthy of note, this Scheme represents essentially a seven step overall synthesis of Epothilone B. Furthermore, Deoxypothilone B **60** may have superior properties to Epothilone B, thus shortening the route to 6 steps.

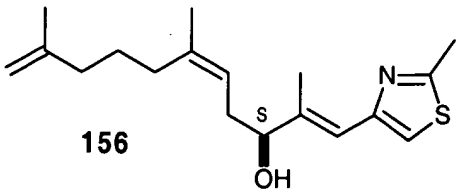
As shown in Figure 24 (Scheme XXIV), another related approach beginning with dihydro-α-myrcene **146** (Rienaecker, R., *.alpha.-Rhodinol and .alpha.-citronellol from*

optically active cis-pinane. Chimia, 1973. **27**(2): p. 97-9), involves the opening of epoxide **141** by a vinylalane. This strategy is analogous to the conversion of **81** to **82** in Figure 15 (Scheme XV). Selective cleavage of the terminal monosubstituted double bond of monoterpene **146** by a suitably hindered, ligated OsO_4 species (such as ADmix-α) (Morikawa, K., *et al., Catalytic Asymmetric Dihydroxylation of Tetrasubstituted Olefins.* J. Amer. Chem. Soc., 1993. **115**: p. 8463-8464; Andersson, P.G. and K.B. Sharpless, *A Dramatic Ligand Effect on the Relative REactivities of Substituted Alkenes with Osmium Tetroxide.* J. Amer. Chem. Soc., 1993. **115**: p. 7047-7048) in the presence of a reoxidant such as $NaIO_4$ should lead directly to the aldehyde **147**. Schroder, M., *Osmium Tetroxide Cis Hydroxylation of Unsaturated Systems.* Chem. Rev., 1980. **80**: p. 187-213. Its reduction to alcohol and protection as a TBS ether should be straightforward in providing **148**. Now, ozonolytic cleavage of the disubstituted terminal double bond of **148** should provide ketone **149** in one pot. Introduction of the vinyl iodide by Wittig reaction is precedented, giving the *Z*-iodide **150**. Now, metallation and in situ transmetallation with an alkyl aluminum chloride should give a vinyl alane intermediate, capable of opening epoxide **141** to give an aluminum alkoxide corresponding to **151**. *In situ* silylation of this intermediate should then give **151** in a one pot procedure starting from **150**. Finally, desilylative oxidation of the protected alcohol in **151** can be achieved by quinolinium fluorochromate to furnish the requisite aldehyde **152**. Chandrasekhar, S., K.P. Mohanty, and M. Takhi, *Practical One-Pot Di-O-silylation and Regioselective Deprotective Oxidation of 1-O-Silyl Ether in 1,2-Diols.* J. Org. Chem., 1997. **62**: p. 2628-2629. Now, aldol condensation as before with the trianion of **56a** should lead to production of **59**, which as before can be converted to Epothilone B.

A viable alternative to the iodide **150** of Figure 24 (Scheme XXIV) is shown in Figure 25 (Scheme XXV). The inexpensive industrial chemicals prenyl bromide and MVK can be coupled in one step with Zn/Cu accelerated sonochemically to furnish a well known phermone intermediate, **153**. Trehan, I.R., *et al., Synthesis of undecan-3-one; (.+-.) frontalin; (.+-.)-endo-, and (.+-.)-exo-brevicomin under sonochemical aqueous conditions.* Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem., 1995. **34B**(5): p.

396-8. Wittig reaction of ketone **153** as before should then afford the Z-olefin **154**, chiral hydroboration of which is expected to smoothly give the alcohol-iodide **155**. Finally, protection provides the common intermediate **150** (**148**, R_1 = TBS), also used in Scheme XXIV en route to Epothilone B.

A further scheme for synthesizing epothilones involves an intramolecular aldol condensation instead of the intermolecular approaches outlined above. Generation of the triene **156**:



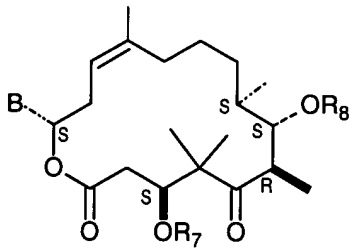
156

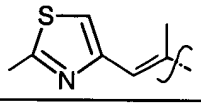
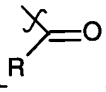
is directly analogous to formation of the silylated derivative **132** except that the reaction is worked up with dilute acid instead of a silyl electrophile such as TBSOTf or TBSCl, giving the alcohol **156** instead. The β-lactone **157** (IR: 1832 cm^{-1}) was prepared directly from the keto-acid alcohol **56** by treatment with $PhSO_2Cl$ and pyridine as shown in Figure 26a (Scheme XXVIa), and should serve as a source of acylating agent for construction of the triene-ketoalcohol construct **158**, as shown in Figure 26b (Scheme XXVIb). Thus, treatment of **156** with **157** in the presence of pyridine or other amines, with DMAP as catalyst, should allow for formation of **158** (R = H). Alternatively (step c in Scheme XXVIb), capture of the final alkoxide intermediate leading to **156** with **157**, instead of the water workup, should give **158** directly in a one pot procedure. Further, the product **158**, either purified, crude, or *in situ* (step c), can be O-alkylated with a variety of reagents such as benzyloxymethyl chloride (BOMCl), p-methoxybenzyloxymethyl chloride (PMBMCl), 2-trimethylsilylethyloxymethyl chloride (SEMCl) or even 3,4-dimethyoxybenzyl chloride (DMBCl), bromide, or trichloroamidate ($Ar\text{-}CH_2O\text{-}C(CCl_3)=NH$). It can also be silylated with any usual silyl reagent such as TMS, TBS, TIPS, etc.

With protected **158** in hand, hydroboration as before with $(Ipc)_2BH$ can be followed by conventional workup to afford alcohol **159**, or the intermediate borane can be directly oxidized with Cr(VI) to afford the aldehyde **160**. Of course, the alcohol **159**

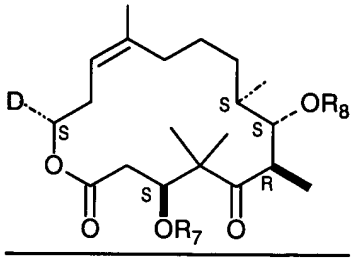
can be oxidized under Swern conditions to furnish **160** as well. Now, selective enolborane formation with a dialkylboron triflate can be effected to give the transient boron enolate **160a** which should undergo intramolecular aldol reaction to afford the cyclized lactone **161**. Finally, removal of the protecting group with appropriate conditions, e.g., when R = PMBM, use of DDQ readily leads to cleavage to deoxyepothilone B, **139**.

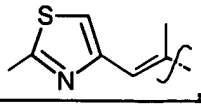
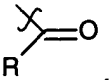
A variety of analogs of **60** can be prepared as outlined in Figure 27 (Scheme XXVII), taking advantage of the greater steric accessibility of the C-3 hydroxyl group. In one case, direct acylation of C-3 provides **162**, leaving only one additional hydroxyl group ~~which could be acylated under more forced conditions to give **163**.~~ Chemical compound **162**, and stereoisomers thereof, may also be represented by the general formula



where B is  ; R_7 is  ; and R_8 is H.

Chemical compound **162** can be acylated under more forced considtions to give **163**. Chemical compound **163**, and stereoisomers thereof, can be generally represented by the formula



and stereoisomers thereof, where D is  , R_7 is  ,

R_8 is  . Alternatively, silylation of C-3 furnishes **164**, and forced acylation then gives **165** after silica gel purification to simultaneously remove the TMS group from C-3. In these reactions, R = alkyl, aryl, alkyl-aryl, OR, NRR', SR, and so on. In addition, the X group in RCOX denotes the use of active esters to effect these transformations as well as acid chlorides, and in some cases may suggest the use of isocyanates, thioisocyanates, etc.

Another approach to producing analogs of epothilones was outlined in Figure 28 (Scheme XXVIII). Here, a generally applicable synthetic route to epothilones and their analogs is shown. The process entails the novel Normant reaction of a Grignard reagent **B** (where R can be H, Me or a variety of aryl, alkyl or other moieties) with a terminal alkyne **C** (where R can be H, Me or a variety of aryl, alkyl or other moieties); the resulting intermediate is then treated with an alkynyl lithium to produce an alkenyl-mixed cuprate **BC** which is quenched by a protected 1,2-epoxy-3-hydroxy species **A** (where R can be H, Me or a variety of aryl, alkyl or other moieties). The intermediate or crude product is then treated with an alcohol protecting group reagent (such as a SEM chloride, i.e. a 2-silylethoxymethoxy chloride), producing in a single operation, the diene **D**.

The diene **D** can either be hydroformylated under chiral conditions, or hydroborated using bis(isopinocampheyl)borane to furnish ultimately the aldehydes **E** or **F**. In the case of **F**, the PMB protecting group is removed, the alcohol is oxidized, and the ketone made to undergo Horner-Emmons reaction to install the vinylic aromatic species, such as **F**.

With either aldehyde **E** or **F**, aldol condensation of the dianion prepared from **10** followed by protection of the resulting aldol derived, β-hydroxy group as an acyl derivative (e.g. the TROC group; trichloroethoxycarbonyl or Cl_3CCH_2OCO-; or for example, a hexenoyl moiety; e.g. CH_2=$CH(CH_2)_3CO$-), leads to formation of the

diastereomeric aldol adducts **G** or **H**. In the case of **H**, simple cleavage of the C-15 protecting group (when SEM, use a fluoride source such as HF•pyridine) can be achieved. After lactonization, the diprotected lactone **J** is obtained. Removal of the remaining silicon protecting group gives an epothilone D analog that can be epoxidized to give an epothilone B analog. Alternatively, norepothilone analogs that mirror the **H** manifold, **I**, can be obtained by derivatization of the C-16 hydroxyl group with R_7. As before, the silicon group can be removed to give a norepothilone D analog, epoxidation of which would give a norepothilone B analog.

In any case, R_1 can be **H** for the epothilone A series, or another group to provide an entirely new species.

After removal of the TBS group from **I** or **J**, an additional acyl group can be installed to give **K** or **L**. When the COR_3 group is a proctecting group like a TROC, it can be removed from **K** or **L** to give **M** or **N**. These chemistries allow for the hydroxyl groups to be derivatized in any pattern desirable to achieve the required pharmacological properties of the materials. For example, in the case of **N**, when R_4, R_2, R_1, R = Me, R_3 = H, and R_6 = CH_2=CH(CH_2)$_3$CO-, an analog of epothilone is produced by total synthesis, but never via the natural product. The side-chain double bond can be selectively cleaved to allow formation of an aldehyde that can be used as a tether to solubilizing groups, etc.

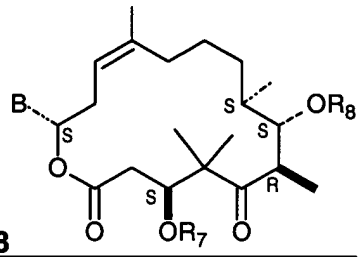
As above, protecting groups can be manipulated to arrive at structures such as M with a variety of substituents. These substituents can be optimized by combinatorial or parallel synthesis methods to provide norepothilone analogs optimized for high anticancer potency and minimized toxicity. Addtional approaches to targeting these analogs could involve tethering to carrier molecules.

In more detail, a specific example is provided in Figure 29 (Scheme XXIX). The Normant product **166** was protected as SEM ether to give **167**. The PMB group was deprotected by using DDQ and the resulting alcohol was oxidized to the corresponding ketone **169** which was then reacted with Horner-Emmons reagent **24** to furnish triene **170**. Hydroboration of compound **170** with bis(isopinocampheyl)borane and oxidative work up with hydrogen peroxide gave the *S*-methyl alcohol **171**. Oxidation of alcohol

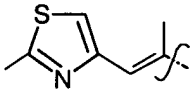
171 afforded aldehyde **172**. The ensuing aldol condensation of **172** with ketoacid **10** gave products **173a** and **173b** in 1:1 ratio. Hydroxy acids are protected as TROC esters and SEM group was deprotected and subsequent macrolactonization afforded **174**. Removal of protecting groups gave desoxyepothilone B.

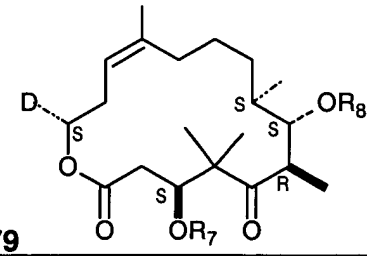
The particulars of Figure 29 (Scheme XXIX) allow for entry to previous Scheme XXVII (Figure 27), in which **178** is similar to **165**. Similarly, **174** can lead to the homolog of **164** in which the Si group is a TBS instead of a TMS. The TROC **165** can be acylated at C-3, and the TROC removed to give **162** and thereby **163**. This is shown in Figure 30 (Scheme XXX). An acyl group is installed at C3 of **178** to give **179**. The TROC can be removed to give **180**. Finally, another acyl group can be added to C7 to give a diacyl derivative **181**, itself available from the alternate manifold culminating in **184**. Along these lines, the TROC can be removed to afford **182** and the C7 hydroxy acylated to give **183**. Removal of the TBS group should give **184**.

With continued reference to Figure 29 (Scheme XXIX), chemical compounds **178** to **181**, and stereoisomers thereof can also be represented as the following general formulas:

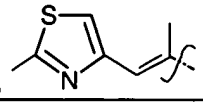


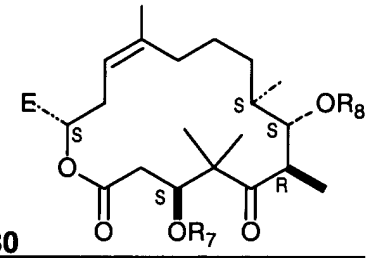
178

where B is  and, R_7 is H and R_8 is TROC.

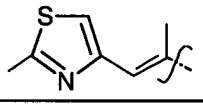


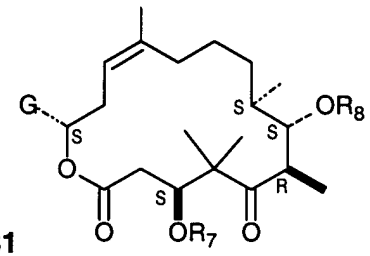
179

where D is  and R_7 is COR_1 and R_8 is TROC.

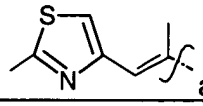


180

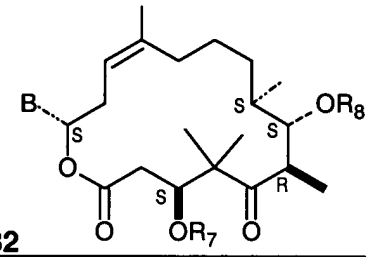
where E is  and R_7 is COR_1 and R_8 is H.



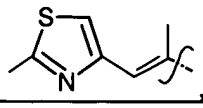
181

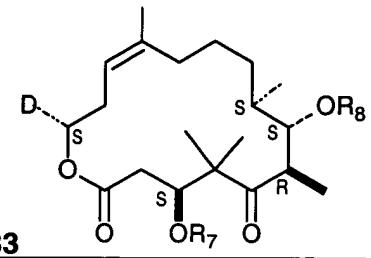
where G is  and R_7 is COR_1 and R_8 is COR_2.

Similarly, chemical compounds **182-184**, and stereoisomers thereof, can be represented as the following general formulas:

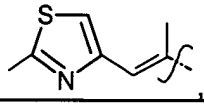


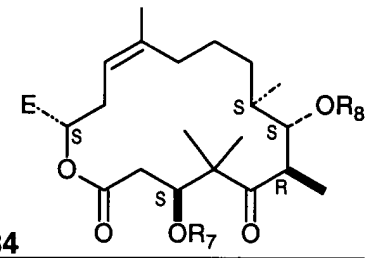
182

where B is  , R_7 is TBS, and R_8 is H.

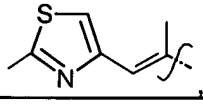


183

where D is  , R_7 is TBS, and R_8 is COR_2.



184

where E is  , R_7 is H and R_8 is COR_2.

A specific example is afforded in Figure 31 (Scheme XXXI), in which a hexenyl moiety is pendant to the C7 hydroxyl group. In this case, after the aldol reaction, the intermediate is quenched with hex-5-enoic acid active ester or the acid chloride to give **185**. This is similar to the TROC derivitization giving **173**. As before, selective SEM removal affords **186**. After lactonization, **187** is formed, from which the TBS can be removed with HF•pyridine to give **188**. Finally, the side chain olefin (least hindered) can be hydroxylated and cleaved affording the aldehyde **189**. Alternatively, a hexanoic acid

ester derivative may instead be used, e.g. by replacing $CH_2=CH(CH_2)_3COCl$ in step a of Figure 31 with $CH_3(CH_2)_4COCl$ and leaving out steps e and f. The use of other alkanoic or alkenoic acid esters, substituted and unsubstituted, is also contemplated.

A further route to the epothilones is demonstrated with respect to Figures 32 through 37. The *Z* olefin, an essential feature for the synthesis of epothilone B, as reported in the literature, was prepared either by classical Wittig olefination methods or ring closing olefin metathesis approaches. Herein we report a unique and stereoselective method to generate the trisubstituted *Z* olefin geometry by modification of a classical Normant alkyne cupration and electrophile trap.

Retrosynthetic disconnection of epothilone B indicated to us that synthons **203** and **204** could serve as key intermediates, which could be coupled together via a double-diastereoselective aldol condensation, as shown in Figure 32 (Scheme XXXII) and macrolactonization to furnish the target framework. The synthesis of aldehyde unit **203**, the northern hemisphere of epothilone B, is based on the retrosynthetic strategy indicated in Figure 33 (Scheme XXXIII). Thus, ring opening of epoxide **205** by the Normant-derived vinyl cuprate **206**, should lead to an alcohol whose oxidation to ketone could be followed by a Wadsworth-Emmons olefination reaction. Finally, the α-methyl carboxaldehyde could be generated by a chiral hydroboration-oxidation sequence to provide **203**.

The synthesis of fragment **203** was commenced by protection of (2*S*, 3*R*)-1,2-epoxy-3-butanol **208** as its *p*-methoxybenzyl (PMB) ether, as shown in Figure 34 (Scheme XXXIV). This was achieved by treating compound **208** with sodium hydride and PMB bromide to give **205** in 85% yield. Hetakeyama, S.; sakurai, K.; Takano, S. *Heterocycles*, **1986**, *24*, 633-637. The Normant coupling reaction with epoxide **205** was performed conveniently as follows. Normant, J. F. *Synthesis* 1972, 63-80; Marfat, M.; McGuirk, P.; R.; Helquist, P.*J. Org. Chem.* **1979**, *44*, 3888- 3092.

After forming the Grignard reagent from the reported bromide **209**, admission of CuBr-DMS complex and stirring for several hours at low temperature led to a black solution of cuprate reagent. Condensation of propyne (*g*) into the cuprate solution at low temperature was followed by addition of lithiohexyne. Alkylation of the resultant

vinyl cuprate **210** was accomplished over the course of one day at -25 °C following addition of epoxide **205**. Chromatography of the crude product provided the diastereomerically pure *Z*-alkene **211** in 76% yield. The alcohol moiety of alkenol **211** was derivatized with SEMCl and DIPEA to provide a SEM-ether, **212**. Removal of the PMB ether of **212** with DDQ left the SEM-ether intact to give the alcohol **213**. Oxidation of **213** was then effected under Swern conditions to afford the methyl ketone **214** in 85% yield. Wadsworth-Emmons olefination of ketone **214** with the known phosphonate **207** led to the production of diastereomerically clean triene **215** in 72% yield. Schnizer, D.; Limberg, A.; Bohm, O. M. *Chem. Eur. J.* **1996**, *11*, 1477- 1482. Finally, diastereoselective hydroboration of the triene **215** using $(i\text{-PC})_2\text{BH}$ (Wifely, G.; Ayyangar, N. R.; Takashi Munekata.; Brown, H. C..*J. Am. Chem. Soc.* **1964**, *86*, 1076-1078; Brown, H. C.; Joshi, N. N. *J. Am. Chem. Soc.* **1988**, *53*, 4059- 4061) followed by oxidative work-up and subsequent Swern oxidation of the resulting alcohol **216**, furnished the enantiomerically pure aldehyde **203** in 92% yield.

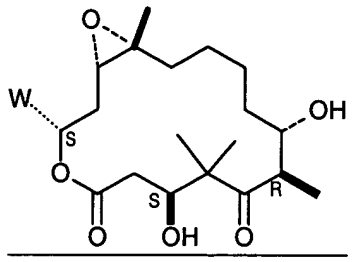
For the aldol condensation shown in Figure 32 (Scheme XXXII), the silyl protected keto-acid **204** was required. This acid could be prepared as reported in our work via an Evans enantioselective aldol condensation. Panicker, B.; Karle, J. M.; Avery, M. A. *Tetrahedron*, **2000**, *56*,7859-7868 and references therein. As shown in Figure 35 (Scheme XXXV), the dibutylboron enolate of the reported oxazolidinone **217** reacted with keto-aldehyde **218** to give an α-thiomethyl amide aldol intermediate. Desulfuration was readily accomplished using Raney Ni, providing the corresponding *R*:*S* aldol adducts **219** in a 23:77 ratio, respectively (70% yield). After silylation with TBDMSOTf and removal of auxiliary, we obtained **204** in good overall yield.

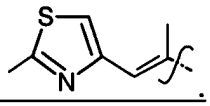
The optimum conditions for the aldol condensation of keto-acid **204** with aldehyde **203** required generation of the dilithio derivative of **204** with LDA (-78 °C to -40 °C) followed by metal exchange with anhydrous $ZnCl_2$ at -78 °C. Nicolaou, K. C.; Winssinger, N.; Pastor, J.; Ninkovic, F.; Sarabia, F.; He, Y.; Vourloumis, D.; Yang, Z.; Li, T.; Giannakaku, P.; Hamel, E. *Nature*, **1997**, *387*, 268- 272. Thereupon, reaction of aldehyde **203** with the transmetallated enolate of **204** led to formation of polar adducts best handled as shown in Figure 36 (Scheme XXXVI). Treatment of the aldol mixture

with 1.2 equivalents of TBSCl and excess TrocCl in pyridine furnished a mixture of fully protected products. Upon exposure to trifluoroacetic acid at –20 °C, deprotection of the SEM ether with simultaneous deprotection of TBS esters occurred. At this stage the aldol product mixture could be conveniently separated from the unreacted keto-acid **204** by flash column chromatography giving adducts **220** and **221** in a 2:1 diastereomeric ratio.

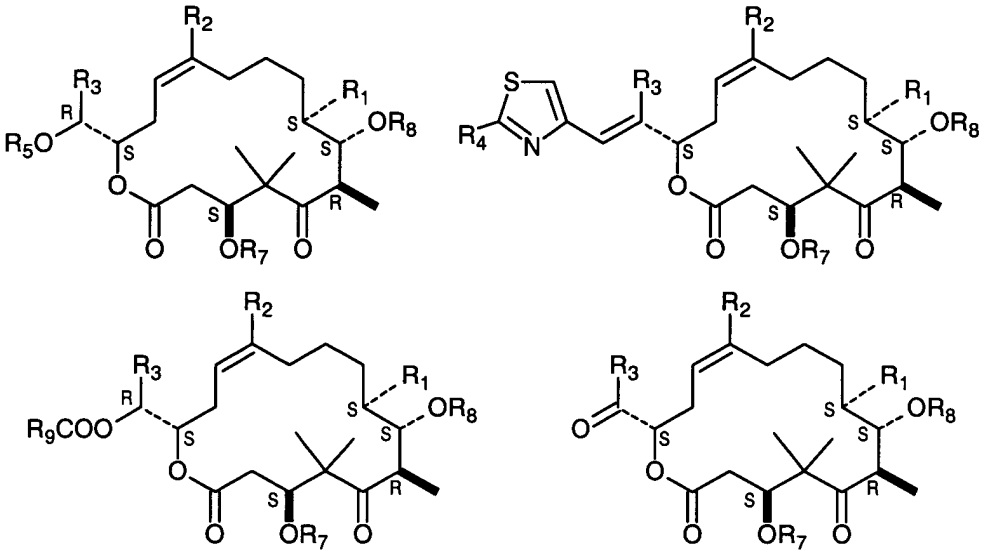
The mixture of hydroxy acids was then subjected to macrolactonization using the Yamaguchi method (Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989) to obtain the corresponding lactones as shown in Figure 37 (Scheme XXXVII). The two lactones **222** and **223** were readily separated by flash column chromatography and **222** was characterized by conversion to natural product. Selective deprotection of the TBS group from **222** using HF-Py followed by chromatographic purification gave the desired Troc-alcohol **224**. Removal of the Troc group was effected using Zn and aq. NH_4Cl in MeOH to provide the diol **225**, epothilone D. Yang, D.; Wong, M.-K.; Yip, Y.-C.; *J. Org. Chem.* 1995, *60*, 3887- 3889. Finally, treatment of **225** with methyl (trifluoromethyl)-dioxirane led cleanly to epothilone B **202**, whose properties were identical to reported spectral and physical data for the natural product. For synthetic Epothilone B **202**, $[\alpha]^{25}_D$ = -31° (*c* 0.25, $CHCl_3$); Reported rotation (Meng, D.; Bertinato, P.; Balog, A.; Su, D.-S.; Kamenecka, T.; Sorensen, E.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1997**, *119*, 100073-10092) for synthetic Epothilone B **2**, $[\alpha]^{25}_D$ = -31° (*c* 0.045, $CHCl_3$).

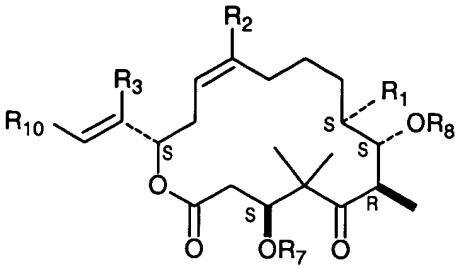
Epothilone B **202**, and stereoisomers thereof, may be represented by the following general formula

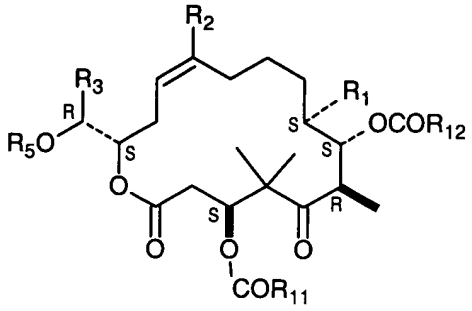


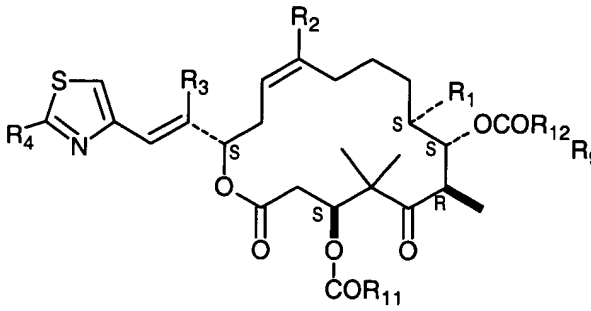
where W is  .

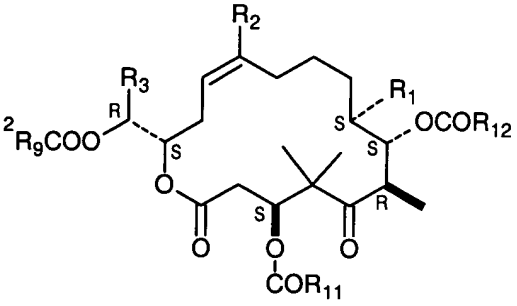
While specific examples have been provided herein of particular chemical compounds formed by specific reaction steps, It should be appreciated that the present invention broadly contemplates numerous variations in the chemical compounds and in the reactants used in any given reaction step, thereby to form various chemical compounds having such substituents as might be desired, as understood by the ordinarily skilled person. For example, the present invention contemplates variations in the protecting groups, such as the use of other types and classes of protecting groups as generally understood by the ordinarily skilled organic chemist. Other variations contemplated by the present invention include variations in the ester moieties at the C-3 and C-7 positions, for example, as well as variations in the sidechain structures and substituents thereof. For example, the present invention broadly contemplates, without limitation, chemical compounds (and stereoisomers thereof) of the following formulas, among others:

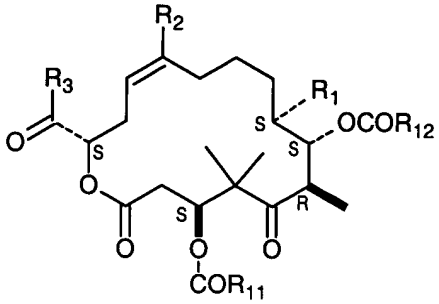


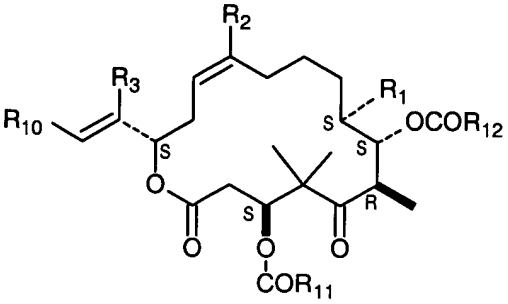


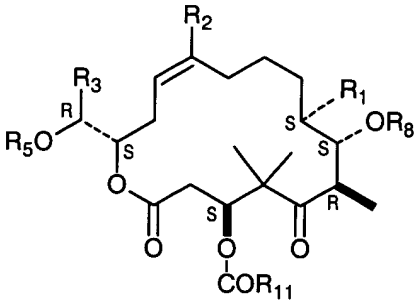


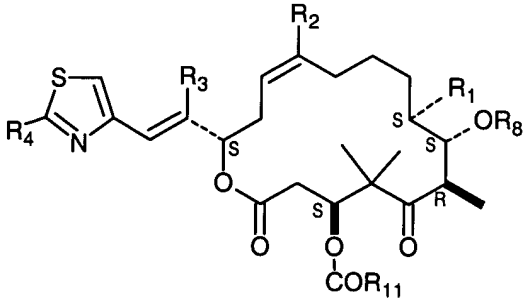


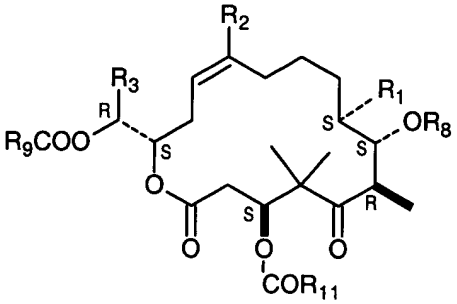


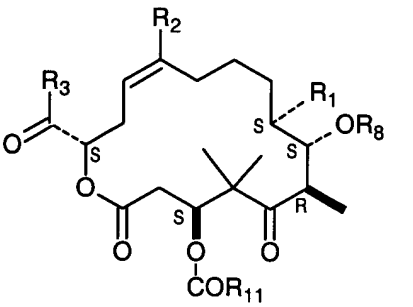












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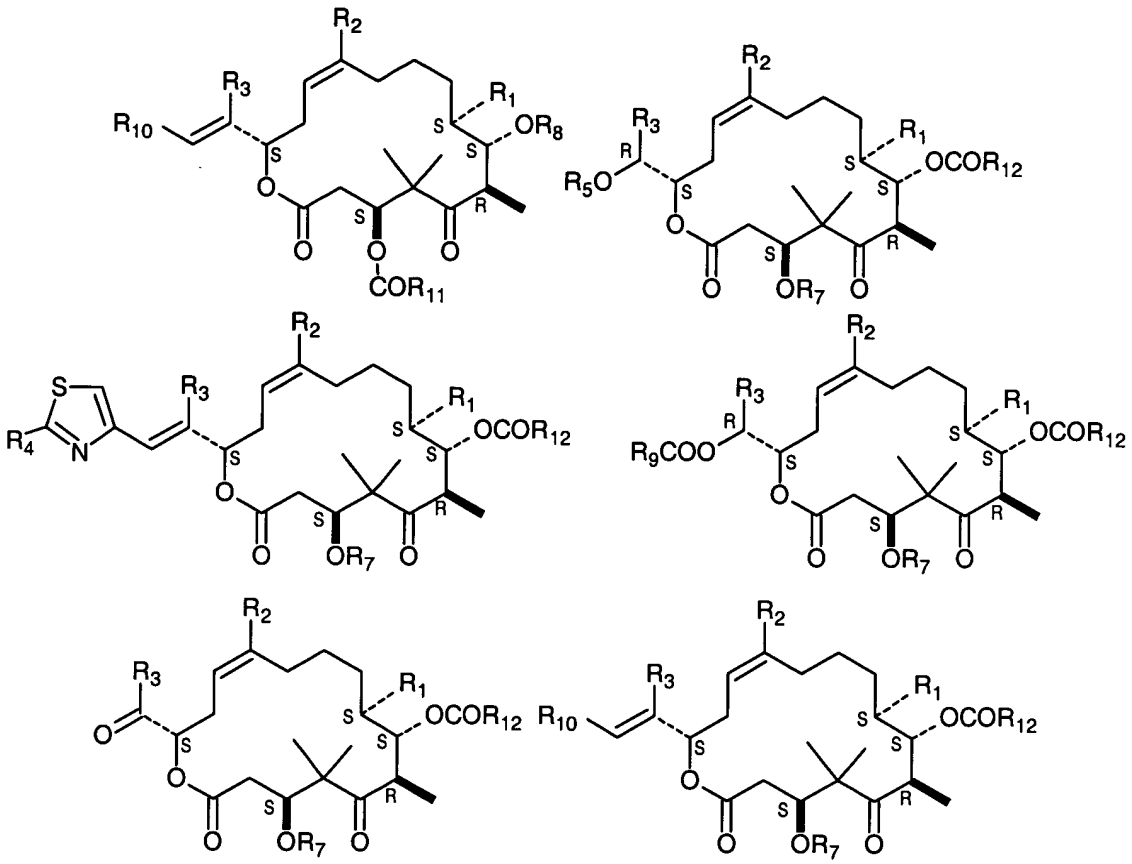
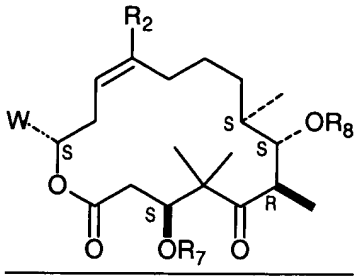


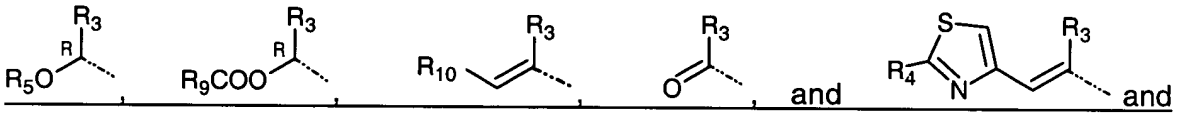
wherein R_1 through R_{12} may be various substituents selected from the numerous varieties of known possible substituents in the art. For example, R_1, R_2, R_3, R_4, R_9 and R_{10} may be each selected from H, alkyl, alkenyl, alkynyl, aryl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted aryl, cycloalkyl, heterocyclo; R_5, R_6, R_7 and R_8 may be selected from H and a protecting group; and R_{11} and R_{12} may be each selected from alkyl, alkenyl, alkynyl, aryl, alkyl-aryl, alkyloxy, aryloxy, cycloalkyl, heterocyclo, amino, sulfo, and substitutions thereof. It is contemplated that R_{11} and R_{12} may be respectively selected such that the 3 and 7 positions may form various desired esters, and in particular esters of alkanoic and alkenoic acids, such as hexanoic and hexenoic acids (e.g., R_{11} or R_{12} may be $-(CH_2)_xCH_3$, $-(CH_2)_yCH=CH_2$, and the like where x and y are appropriate integers, such as 3 or 4. These substituents may be further substituted as understood in the art. It should further be understood that various

appropriate intermediate compounds may thus be formed, such as precursors and compounds for use in, or formed during, the aldol condensation and macrolactonization steps described above, or in the various other conversion steps described herein.

Collectively, the above-identified chemical compounds can be represented by the general formula



where W is selected from



where R_1-R_{12} may be defined as described above.